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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,195	12/03/2003	Shan Lu	17738-003001 / UMMC 03-24	7308

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
10/31/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/728,195	LU ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-60,81-85,88,94,96,100,107 and 111-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-60,81-85,88,94,96,100,107 and 111-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/03/03 & 6/4/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2008, has been entered.

2. In the amendment filed on August 11, 2008, Claims 1-53, 61-80, 86, 87, 89-93, 95, 97-99, 101-106 and 108-110 have been cancelled. New Claims 111-122 have been added. Accordingly, Claims 54-60, 81-85, 88, 94, 96, 100, 107 and 111-122 are pending and are considered in this Office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 54-60, 81-85, 88, 94, 96, 100, 107 and 111-122 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

5. Please note that the newly amended scopes "...(a) at least three and no more than five sets of nucleic acid molecules encoding HIV envelope glycoproteins, ..." (Claim 54); "... at

lease three different clades" (Claim 111) and "... at least four different clades" of Claims 111-114) are NEW MATTER. It is noted that the specification exemplified a method of using multiple sets of HIV *env* DNAs in Examples. However, the specification has not explicitly excluded any specific combinations of HIV *env* DNAs, such as a combination of two or more than five *env* DNAs from different clades. Thus, there is no support for the new limitation of "at least three and no more than five sets of nucleic acid molecules encoding HIV envelope glycoproteins" in the specification. Removal of all new matter is required. Reference: In re Russsmussen 210 USPQ 325.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. (**Prior rejection-withdrawn**) The rejection of Claims 54-60 and 81-110 under 35 U.S.C. 103(a), as obvious over Barnett, Gao and Andre, **is withdrawn** in view of amendment to the claims. The claims have been amended by comprising additional sets of gag DNA in the alleged method of the amendment filed on August 11, 2008. The prior rejection is withdrawn in view of the amendment. New rejection necessitated by the amendment is set forth below.

8. **(New rejection-necessitated by the amendment)** Claims 54-60, 81-85, 88, 94, 95, 100, 107 and 111-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett (Vaccine, Vol. 15 (1997), No. 8, pp 869-873), Nabel (WO 02/032943, International filing date August 14, 2001; and International Publication date April 25, 2002); Gao 1 (*J. Virology* Vol.70 (1996), No.3, pp 1651-1667); Gao F. *et al.* (Meeting Abstract; *AIDS Vaccine 2001.* 2001 Sep 5-8; abstract no. 201); Yoshida T. *et al.* Clin Exp Immunol. 2001 Jun;124(3):445-52; and Evans (Vaccine. 2001 Feb 28;19(15-16):2080-91).

9. Claims 54-60, 81-85, 88, 94, 95, 100, 107 and 111-122 are directed to a method of inducing immune responses in a mammal comprising prime immunizing the mammal with (a) a set of HIV envelope DNAs and (b) a set of HIV gag DNAs, and boost immunizing the mammal with a set of HIV envelope proteins of different clades, wherein one of more DNA vaccines comprise optimized codons.

10. Using BALB/c mice and Guinea pig as animal models, Barnett teaches a method of inducing immune responses using priming immunization with a DNA plasmid vaccine containing envelope genes of primary strains, HIV-1_{US4} **(clade B)** and HIV-1_{CM235} **(clade E)**, and boosted with their proteins. Both humoral and cell-mediated immune responses were tested. Barnett teaches that the DNA prime/subunit protein boost may be a safe and less costly alternative vaccination strategy because of the ability of HIV DNA vaccines to effectively and reproducibly induce immune responses. Barnett does not teach the use of multiple HIV envelope DNAs and proteins of different clades as immunogens.

11. Barnett does not explicitly teach the following embodiments in the method: (1) a set of gag DNAs (Claim 54); (2) one of more of the sets of DNAs comprises optimized codons (Claims

96 and 120); (3) BaL isolate (Claims 115-117); Czm isolate (Claim 119) and adjuvant QS-21 (Claim 122).

12. Nabel (WO 02/032943) teaches a method of inducing an immune response against HIV in a mammal using sets of DNA encoded HIV envelope proteins of Clade A, C and E and a panel of DNA encoded HIV gag (See e.g. Table 1). Nabel also teaches DNA comprised of optimized codons for humans. Nabel shows that the DNA constructs encoding HIV env and gag proteins can induce CTL and antibody responses in mice.

13. Gao 1 (J. Virology) suggests use of a panel of envelope gene constructs from HIV-1 primary isolates of Clade A to G for AIDS vaccine development to target against a broader spectrum of viruses, wherein isolate 92US715 is isolate **B715** of the instant Claim 94 (See e.g. Abstract).

14. Gao F. *et al* teach use of codon-usage optimized *gag* and *env* genes of a prototypic HIV-1 subtype C strain (96ZM651), which is same **Czm isolate** of the instant Claim 119, to improve HIV-1 protein expression in the context of a DNA vaccine (See whole abstract). The optimized *gag* and *env* genes expressed 24 to 532 times more protein following transfection into 293T cells. One set of env DNA constructs (gp140) can induce anti-gp140 antibodies and cellular immune responses in mice, while none of the 5 mice injected with wt gp140 developed detectable responses. Gao F *et al* teach that codon-usage optimization increases HIV-1 gene expression *in vitro* and appears to markedly enhance both humoral and cellular immune responses upon DNA vaccination *in vivo*.

15. Yoshida teaches a method of inducing immune response to HIV in a mammal using DNA encoding HIV envelope from BaL isolate (See e. g. Abstract). Yoshida teaches that that the

combination of DNA vaccination, Ad-Bal vector infection and passive transfer of Ad-Bal-infected DCs can induce strong immunity against HIV-1 Bal.

16. Evan teaches that adjvant QS-21 can enhance immunogenicity of gp120 HIV-1MN protein (rsgp120) immunization in a mammal, See e.g. Abstract. Evan shows that the lymphocyte proliferation and delayed type hypersensitivity skin testing results were superior in the QS-21 recipients compared with the alum recipients at the low antigen doses.

17. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Barnett, Nabel, Gao and Yoshida in order to increase the breadth of reactivity of a HIV vaccine cross genetic clades and increase the immunogenicity of the vaccine. One would have been motivated to do so, given the suggestion by Gao that envelope genes from HIV-1 Clades A to G should prove valuable for AIDS vaccine development efforts targeted against a broader spectrum of viruses. There would have been a reasonable expectation of success that the polyvalent vaccine and codon optimized immunogen would generate enhanced immune responses, given the knowledge taught by Gao F. that codon optimized DNA vaccines have higher expression level *in vivo* and result in increased immunogenicity of DNA vaccines.

> MPEP § 2144.06 recites the conclusions of *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA), "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art."
>
> The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

18. Since the instant invention is drawn to combining some envelope genes and proteins of known HIV isolates to increase immune responses in a mammal, the combination of their additive effects renders the invention *prima facie* obvious and does not exhibit an unexpected result. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response to Applicant's arguments:

19. Applicant argues that the cited references do not teach or suggest the specific combination and number of DNA and protein vaccines recited in the claims as presently amended (Emphasis added by applicants). The instant specification has shown in Examples 8 and 9 that an 8-valent composition is less effective than a 3-valent composition. Thus, the applicants assert that skilled practitioners would not have expected the using the recited compositions could successfully induce immune responses against HIV.

20. Applicants' argument is considered, but found not persuasive. First, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). According to M.P.E.P. § 2143.02, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F2d 1048, 189 USPQ 143 (CCPA 1976)." In the present case, the cited reference have taught one of skill in the art that the alleged method steps: DNA

priming and protein booting immunization, and all the compositions of HIV env and gag. The cited references have explicitly suggested to use a combination of HIV Clades A to G as multiple (or polyvalent) vaccine composition. The cited references have also shown that one of ordinary skill in the art is capable of testing vaccine compositions, either 2-valent or multiple 1-valent compositions, in animals. Thus, it is within the knowledge of one of ordinary skill in the art to optimize specific combinations of multiple HIV strains as a alleged vaccine using routine laboratory practice. Moreover, Examples 8 and 9 have shown that in rabbits, both 3-valent and 8-valent compositions can induce antibody responses, which is consistent with the teachings of the prior art. Thus, Applicant has not presented any evidence showing that there was no reasonable expectation of success in using the approach and the compositions taught by the prior art references.

Remarks

21. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/B.P./
Examiner, Art Unit 1648